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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/455,952	12/07/1999	GEORGE MICHALOPOULOS	A32516	5777

21003 7590 06/18/2002

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NEW YORK, NY 10112

EXAMINER

NAFF, DAVID M

ART UNIT	PAPER NUMBER
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1651

DATE MAILED: 06/18/2002

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No. 9/45595	Applicant(s) MICROLOGICAL CORP
Examiner Haff	Group Art Unit 1651

—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—

Period of Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

- ☒ Responsive to communication(s) filed on 4/1/00
- ☒ This action is **FINAL**.
- ☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

- ☒ Claim(s) 1-19 is/are pending in the application.
- ☐ Of the above claim(s) 8-11, 13 + 15-19 is/are withdrawn from consideration.
- ☐ Claim(s) _____ is/are allowed.
- ☒ Claim(s) 1-7, 12 + 14 is/are rejected.
- ☐ Claim(s) _____ is/are objected to.
- ☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

- ☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
- ☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
- ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
- ☐ The specification is objected to by the Examiner.
- ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119 (a)-(d)

- ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).
 - ☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been received.
 - ☐ received in Application No. (Series Code/Serial Number) _____
 - ☐ received in this national stage application from the International Bureau (PCT Rule 1.7.2(a)).

*Certified copies not received: _____

Attachment(s)

- ☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____
- ☐ Interview Summary, PTO-413
- ☐ Notice of Reference(s) Cited, PTO-892
- ☐ Notice of Informal Patent Application, PTO-152
- ☐ Notice of Draftsperson's Patent Drawing Review, PTO-948
- ☐ Other _____

Office Action Summary

The amendment of 4/1/02 has been entered. The amendment amended claims 1 and 14.

Claims 8-11, 13 and 15-19 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made without traverse in Paper No. 7 (filed 7/19/01).

Claims examined on the merits are 1-7, 12 and 14.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1-7, 12 and 14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the method of claim 1 wherein hepatocytes and nonparenchymal cells of the co-culture are isolated from liver tissue as a mixture, and for the population of population of claim 14 being obtained by this method, does not reasonably provide enablement for another method of providing a combination of hepatocytes and nonparenchymal cells for co-culturing as claimed, and for obtaining the population of claim 14 by another method. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

No enabling description has been provided of how to obtain a combination of hepatocytes and nonparenchymal cells for co-culture as claimed other than as described in the specification in the paragraph bridging pages 14 and 15.

Applicants urge that methods of obtaining hepatocytes and nonparenchymal cells are well known to those of skill in the art and page 14, line 3, to page 15, line 2, of the specification discloses a number of different methods. However, each of these methods involve isolating
5 the hepatocytes and nonparenchymal cells as a mixture from liver tissue.

Claims 1-7 and 12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

10 The claims are unclear by claim 1 (bridging the last two lines) not having clear antecedent basis for "said hepatocytes that retain hepatic function". The claim fails previously require hepatocytes retaining hepatic function. It is suggested that the last line of claim 1 be amended by canceling "that" and inserting -- while retaining --, and
15 after "function" inserting -- of said hepatocytes --.

Claims 1, 2, 4-7, 12 and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mitaka et al (Hepatology 1999) in view of Naughton et al (5,624,840) and Vacanti et al (5,759,830) for the type of reasons set forth in the previous office action of 9/26/01.

20 The claims are drawn to a method of generating a hepatic cell culture by co-culturing hepatocytes and nonparenchymal cells in the presence of growth factors and a matrix coated with at least one biologically active molecule that promotes cell adhesion, proliferation or survival under conditions sufficient to allow for the proliferation of
25 the hepatocytes while retaining hepatic function of the hepatocytes.

Also claimed (claim 14) is a population of matrix/hepatic cell clusters.

Mitaka et al disclose obtaining hepatic cells and nonparenchymal cells from liver tissue and culturing the hepatic cells and nonparenchymal cells together for hepatic organoid reconstruction.

5 Naughton et al disclose growing stromal cells on a three-dimensional matrix such as made from nylon or polystyrene (col 8, line 1) which may be coated with collagen (col 8, line 8) to form a three-dimensional stromal matrix (col 8, lines 30-40), and then growing hepatocytes on the stromal matrix to form tissue having liver function (col 11, lines 54-
10 57).

Vacanti et al disclose growing hepatocytes (col 6, line 28) in a three-dimensional fibrous scaffold to form tissue having liver function for implanting (col 5, line 35 to col 6, line 62, and col 12, lines 17-47). The fibers of the scaffold may be coated with collagen to enhance
15 cell attachment (col 10, lines 44-47), and epithelial cells may be attached to the scaffold in combination with the hepatocytes (col 12, lines 25-27).

It would have been obvious to carry out the culturing of hepatic cells and nonparenchymal cells together as disclosed by Mitaka et al on a
20 three-dimensional matrix or scaffold as suggested by Naughton et al and Vacanti et al to obtain the function of the matrix or scaffold in producing tissue having liver function. The claims do not exclude the matrix containing stromal tissue as disclosed by Naughton et al.

Moreover, it would have been obvious to grow hepatocytes directly on the
25 matrix without first forming stromal tissue when the function of stromal

tissue is not needed, and since it is clear from Vacanti et al that stromal tissue can be omitted.

Applicant's arguments filed 4/1/02 have been fully considered but they are not persuasive.

5 Applicants urge that a Declaration by Michalopoulos and Bowen states that a manuscript was submitted prior to the date of Mitaka et al. However, to antedate Mitaka et al by asserting priority, a 131 Declaration in proper form is required. The declaration submitted is not a 131 Declaration, and does not contain statements and evidence needed in
10 a 131 Declaration.

Applicants' arguments concerning the references are unpersuasive, since the invention becomes obvious when the reference are taken together as a whole and not when each reference is considered alone.

Claim 3 is rejected under 35 U.S.C. 103(a) as being unpatentable
15 over the references as applied to claims 1, 2, 4-7, 12 and 14 above, and further in view of Matsui et al (5,298,615).

The claim requires the matrix to be in the form of polystyrene beads.

Matsui et al disclose that it is standard procedure to culture
20 animal cells on microcarriers such as polystyrene beads coated with collagen (col 2, lines 10-25).

When using a matrix or scaffold as suggested by Naughton et al and Vacanti et al to culture the cells of Mitaka et al as set forth above, it would have been obvious to provide the matrix or scaffold in the form of
25 polystyrene beads coated with collagen as suggested Matsui et al

disclosing the use of such beads as being a standard technique for culturing animal cells.

Comments set forth above in response to arguments also apply to this rejection.

5 **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of
10 this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the
15 statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David M. Naff whose telephone number is (703) 308-0520. The examiner can normally be reached on
20 Monday-Thursday and every other Friday from about 8:30 AM to about 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, a message can be left on voice mail.

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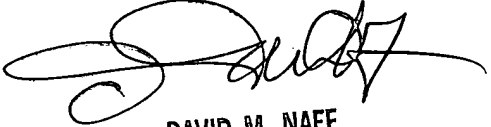
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mike Wityshyn, can be reached at telephone number (703) 308-4743.

The fax phone number is (703) 872-9306 before final rejection or
5 (703) 872-9307 after final rejection.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

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DMN
6/17/02


DAVID M. NAFF
PRIMARY EXAMINER
ART UNIT 1651